REMARKS

Interview request

Applicants respectfully request a telephonic interview after the Examiner has reviewed the instant response and amendment. Applicants request the Examiner call Applicants' representative at 858 720 5133.

Status of the Claims

Pending claims

Claims 42 to 55, 93 to 104 are pending.

Claims added in the instant amendment

In the present response, new claims 105 to 111 are added. Accordingly, after entry of the instant amendment, claims 42 to 55, 93 to 111 will be pending and under examination.

The Restriction Requirement

The Patent Office alleged that the pending claims of the application are directed to ninety separate and distinct inventions under 35 U.S.C. §121, and required under 35 U.S.C. § 121, inventions (A)-(J), SEQ ID NOS:17-24, 35 and 39, including for each a sequence encoding thereof, or an antibody against it and methods of making and using thereof, respectively. In response to the Restriction Requirement, Applicants elected Group IV, nucleotides group G, claims 42-55, drawn to methods of generating variants of SEQ ID NO:23, or a polynucleotide encoding SEQ ID NO:31, with traverse. Applicants respectfully submitted that the Patent Office should reconsider and allow the rejoinder of nucleotide groups A, B, C, D, F, and J, all transaminases originally derived from the organism *Aquifex*.

Outstanding Rejections

Claims 42 to 55, 93 and 94 remain rejected and claims 95 to 104 are newly rejected under 35 U.S.C. §112, first paragraph, written description requirement. Claims 42 to 55 and 95 to 104 are newly rejected under 35 U.S.C. §112, first paragraph, enablement requirement. Claims 42 to 55 and 96 to 103 stand rejected under 35 U.S.C. §112, second paragraph. Claims 42 and 93 remain rejected under 35 U.S.C. §102(b) as allegedly anticipated by Henner, et al. (1986) Gene

49:147-152 (hereinafter "Henner"). Claims 42 to 55, 93 and 94 remain rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Henner in view of Short, U.S. Patent No. 5,939,250, issued August 17, 1999, filed May 22, 1996 (hereinafter "Short"). Applicants respectfully traverse all outstanding objections to the specification and rejection of the claims.

Support for the Claim Amendments

Support for the claim amendments can be found throughout the specification. For example, support for claims directed to methods for generating variants of parent nucleic acids having various sequence identities to exemplary sequences of the invention can be found, inter alia, in paragraph 58, page 11, paragraphs 178 and 179 on pages 42 and 43, and paragraph 229, page 56, of the specification. Accordingly, Applicants respectfully submit that no new matter is introduced by the instant amendments.

Information Disclosure Statement

Applicants thank the Examiner for considering and initialing the Form PTO 1449/ Information Disclosure Statement.

Objections to the specification

The disclosure is objected to for various informalities. The instant amendment addresses this issue.

Objections to the claims

The claims are objected to for various informalities. Applicants acknowledge that the terms "transaminase" and "aminotransferase" mean the same activities. The instant amendment addresses this issue.

Issues under 35 U.S.C. §112, first paragraph

Written Description issues

Claims 42 to 55, 93 and 94 remain rejected and claims 95 to 104 are newly rejected under 35 U.S.C. §112, first paragraph, written description requirement.

The Patent Office remains concerned that a single representative species of the genus of nucleic acids used in the claimed methods may not be sufficient to describe that genus (see, e.g., the instant office action, page 4, first paragraph, and the office action of June 17, 2003, page 7, lines

8 to 12). The instant amendment addresses this concern. For example, amended claims 93 and 95 are now directed to methods using nucleic acids comprising sequences having at least 70% sequence identity to a sequence as set forth in SEQ ID NO:23, or a nucleic acid encoding an amino acid sequence as set forth in SEQ ID NO:31, and their complementary sequences.

The Patent Office also remains concerned that the claims are drawn to a method of generating a variant nucleic acid of unknown structure encoding a transaminase (see, e.g., the instant office action, page 3, last sentence, and the office action of June 17, 2003, page 7, lines 5 to 6). The Patent Office is concerned that the *end products* of the methods may need to be described in the specification. However, Applicants respectfully aver that because the starting products (genus of nucleic acids) of the methods are adequately described, the specification satisfies the written description requirement of section 112 for those methods. The claimed methods generate variant nucleic acids encoding polypeptides having an aminotransferase using starting materials (nucleic acids) sufficiently described in the specification such that one of ordinary skill in the art would be able to ascertain the scope of the claims with reasonable clarity and recognize that Applicants were in possession of the claimed invention at the time of filing. Accordingly, because the *starting products* of the methods are adequately described, the specification satisfies the written description requirement of section 112.

Regarding the starting products, or the genus of nucleic acids modified by the claimed methods, the Patent Office remains concerned that the specification fails to describe any other representative species of the genus by any identifying characteristics or properties other than functionality (see, e.g., the instant office action, page 4, first paragraph). However, the specification *does* describe the genus used in the methods by characteristics or properties other than functionality. The genus has been described in terms of structure (the exemplary nucleic acid SEQ ID NO:23, or encoding SEQ ID NO:31) and physico-chemical properties (e.g., percent sequence identity) in addition to function (e.g., encoding polypeptides having transaminase activity). Applicants respectfully submit that describing a genus of polynucleotides in terms of structure (e.g., exemplary sequence), physico-chemical properties (e.g., % sequence identity) and function satisfies the written description requirement of section 112, first paragraph.

As discussed in Applicants' previous response, Example 14 of the Guidelines concluded that a claim reciting variants claimed by sequence identity to a sequence (specifically, "A protein having SEQ ID NO:3 and variants thereof that are at least 95% identical to SEQ ID NO:3 and catalyze the reaction of A → B) satisfies the written description requirement of section 112, first paragraph. The USPTO guidelines recognize that the written description requirement is met for a genus of polynucleotides described by structure (e.g., an exemplary sequence), a physico-chemical property (e.g., a % sequence identity or stringent hybridization) and a defined function. Applicants respectfully aver that these guidelines apply to the claimed invention, i.e., they recognize that claims directed to a genus of polynucleotides described by an exemplary sequence, a % sequence identity (e.g., at least 70%, 80%, 90% or more sequence identity) and a defined function (e.g., transaminase activity) meet the written description requirement.

The Patent Office also is concerned that the specification does not identify structural characteristics distinguishing aminotransferases encoded by nucleic acids used in the claimed methods (see, e.g., page 5, lines 6 to 8, of the instant office action). However, the USPTO guidelines recognized that the written description requirement is met for a genus of polynucleotides described by structure (e.g., an exemplary sequence), a physico-chemical property (e.g., a % sequence identity or stringent hybridization) and a defined function, without setting forth any requirement that the specification must disclose any specific structural characteristics or elements distinguishing the claimed activity (e.g., a transaminase activity) to reasonably describe the genus. Accordingly, Applicants respectfully submit that it is not necessary to set forth any *additional* specific structural characteristics or elements distinguishing the claimed activity (transaminase activity) to reasonably describe the genus (noting that a specific structural characteristic reasonably describing the genus of nucleic acids used in the claimed methods has been described, e.g., a genus of polynucleotides is described by structure (exemplary sequence), a physico-chemical property (a % sequence identity or stringent hybridization) and a defined function.

Furthermore, one skilled in the art could have identified common structural characteristics distinguishing aminotransferases encoded by nucleic acids used in the claimed methods by simply aligning disclosed exemplary sequences of the invention to each other, as illustrated in Exhibit A, or to known transaminase sequences. Exhibit A shows a sequence

alignment among SEQ ID NOs 23 and 31, relevant to the claims in this application, and several other aminotransferases disclosed in this application.

34AT2_001 SEQ ID NOs: 23, 31 (relevant to the claims in this application)

3AT2_001 SEQ ID NOs: 35, 36

34AT5_001 SEQ ID NOs: 18, 26

34AT6_001 SEQ ID NOs: 39, 40

3AT1_001 SEQ ID NOs: 21, 29

(consensus sequence)

The sequence alignment shown in Exhibit A illustrates that the exemplary sequence of the invention (SEQ ID NO:31) used in the claimed methods has a plurality of shared sequences to other nucleic acids encoding polypeptides having transaminase activity. As declared by Dr. Short, at the time of the invention aligning sequences was a routine method for comparing sequences to identify common structural characteristics (e.g., sequences, motifs) related to a function, for example, aminotransferase activity. Dr. Short declares that one skilled in the art could have aligned and compared the disclosed exemplary sequences of the invention to each other or to known transaminase sequences to determine common, specific structural characteristics reasonably related to the genus of transaminases used in the claimed methods, e.g., as illustrated in Exhibit A.

Dr. Short declares that assays such as high through-put enzyme activity screening known at the time of the invention made methods that required previous knowledge of specific structural characteristics (e.g., protein structure, including secondary or tertiary structure, active site sequences, and the like) obsolete and unnecessary. Dr. Short declares that assays such as high through-put enzyme activity screening known at the time of the invention made methods that required previous knowledge of how structure correlates with function obsolete and unnecessary to practice the claim invention.

The Patent Office also is concerned that the reaction that is catalyzed (the reaction defining the function of the genus of nucleic acids used in the claimed methods) is unknown because transaminases catalyze numerous different reactions (see, e.g., the sentence spanning pages 15 and 16, of the instant office action). However, Applicants respectfully aver that because transaminases and transaminase screening assays were well known in the art at the time of the

invention, using the teaching of the specification, one of ordinary skill in the art would have been able to ascertain the scope of the claimed genus of transaminase-encoding nucleic acids with reasonable clarity, and recognize that Applicants were in possession of the claimed invention at the time of filing. As noted in the attached expert declaration by Dr. Jay Short, who was an expert in the field of molecular biology and enzyme development at the time of the invention, Dr. Short declares that procedures for identifying nucleic acids that encode transaminase were conventional and routine in the art at the time of the invention. Dr. Short declares that procedures for identifying polypeptides having any transaminase activity (including enzymes capable of catalyzing the transfer of amino groups from α-amino to α-keto acids) were conventional and routine in the art at the time of the invention. Dr. Short declares that transaminase screening assays were routine and well known in the art at the time of the invention. Dr. Short declares that because the different reactions catalyzed by transaminases (aminotransferases), and assays for detecting such activity, were well known in the art at the time of the invention, one of ordinary skill in the art would have been able to ascertain the scope of the genus of transaminase-encoding nucleic acids used in the claimed methods with reasonable clarity and recognize that Applicants were in possession of the claimed invention at the time of filing.

Dr. Short declares that one of ordinary skill in the art using the teaching of the specification could have made and expressed nucleic acids having a percent sequence identity (including 70% sequence identity) to an exemplary nucleic acid, and could have determined, using routine screening and with predicable positive results, which of those nucleic acids encoded a transaminase. Dr. Short declares that using the teaching of the specification one of ordinary skill in the art would have been able to ascertain the scope of the claimed genus of transaminase-encoding nucleic acids with reasonable clarity and recognize that Applicants were in possession of the claimed invention at the time of filing.

Accordingly, Applicants respectfully submit that the pending claims meet the written description requirement under 35 U.S.C. §112, first paragraph. In light of the above remarks, Applicants respectfully submit that amended claims are sufficiently described in the specification to overcome the rejection based upon 35 U.S.C. § 112, first paragraph.

Enablement

Claims 42 to 55 and 95 to 104 are newly rejected under 35 U.S.C. § 112, first paragraph, enablement requirement.

The Patent Office notes that the specification is enabling for methods of generating a variant transaminase comprising creating a library of variants of SEQ ID NO:23 or a nucleic acid encoding SEQ ID NO:31 by modifying one or more nucleotides of SEQ ID NO:23, expressing the modified sequence, screening the proteins produced from said modified sequence for transaminase activity and selecting a variant sequence which encodes a protein having transaminase activity.

However, the Patent Office is concerned that a genus of nucleic acids comprising at least 50% sequence identity to the exemplary nucleic acid is so large it might take undue experimentation to make such a genus. The instant amendment addresses this issue. For example, amended claims 93 and 95 are now directed to methods using nucleic acids comprising sequences having at least 70% sequence identity to a sequence as set forth in SEQ ID NO:23, or a nucleic acid encoding an amino acid sequence as set forth in SEQ ID NO:31, and their complementary sequences.

The Patent Office is also concerned that the specification does not describe detailed ways in which the protein's structure (encoded by a nucleic acid used in the methods of the invention) is related to its function. It is alleged, inter alia, that predictability of which changes can be tolerated in a protein's amino acid sequence and obtain a desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification. It is alleged that it would have required some knowledge or guidance as to how structure is related to function to generate the genus of transaminase-encoding nucleic acids used in the claimed methods without undue experimentation.

However, to address these concerns, Dr. Short declares that it would not have required any knowledge or guidance as to how structure is related to function to generate the genus of transaminase-encoding nucleic acids used in the claimed methods without undue experimentation. Dr. Short declares that assays such as high through-put enzyme activity screening known at the time of the invention made obsolete and unnecessary methods that required previous knowledge of protein structure, including secondary or tertiary structure, active site sequences, and the like. Dr. Short declares that assays such as high through-put enzyme activity screening known

at the time of the invention made methods that required previous knowledge of how structure correlates with function obsolete and unnecessary to practice the claim invention.

Dr. Short declares that at the time of the invention, high through-put *in vivo* (e.g., whole cell) nucleic acid expression and enzyme activity screening protocols were well known in the art. Dr. Short declares that transaminase screening assays were well known in the art at the time of the invention. Dr. Short declares that the specification presented to the skilled artisan a rational and predictable scheme for making the genus of transaminase-encoding nucleic acids used in the claim methods, including a rational and predictable scheme for modifying any nucleic acid residue of an exemplary nucleic acid with an expectation of obtaining the desired function. Dr. Short declares that the specification provided sufficient guidance to one of ordinary skill in the art to make and use the claimed genus of nucleic acids or polypeptides to practice the invention.

Furthermore, Dr. Short declares that one skilled in the art could have identified common structural characteristics distinguishing aminotransferases encoded by nucleic acids used in the claimed methods by simply aligning disclosed exemplary sequences of the invention to each other, as illustrated in Exhibit A, or to known transaminase sequences. Dr. Short declares that the sequence alignment shown in Exhibit A illustrates that the exemplary sequence of the invention (SEQ ID NO:31) used in the claimed methods has a plurality of shared sequence to other nucleic acids encoding polypeptides having transaminase activity. Dr. Short declares that at the time of the invention, aligning sequences was a routine method for comparing sequences to identify common structural characteristics (e.g., sequences, motifs) related to a function, for example, aminotransferase activity. Dr. Short declares that one skilled in the art could have aligned and compared the disclosed exemplary sequences of the invention to each other or to known transaminase sequences to determine common, specific structural characteristics reasonably related to the genus of transaminases used in the claimed methods, e.g., as illustrated in Exhibit A.

Dr. Short declares that procedures for modifying and expressing nucleic acids were conventional and routine in the art at the time of the invention. Dr. Short declares that procedures for determining the activity of the expressed modified nucleic acids and determining if the nucleic acids expressed a polypeptide with transaminase activity were conventional and routine in the art at the time of the invention. Dr. Short declares that procedures for determining sequence identity to an

exemplary nucleic acid were routine in the art at the time of the invention. Dr. Short declares that procedures for expressing and screening for transaminase activity were conventional and routine in the art at the time of the invention.

Dr. Short declares that one of ordinary skill in the art using the teaching of the specification would have been able to make and use the genus of compositions used in the methods of the invention, including a genus of transaminase-encoding nucleic acids having at least 70% sequence identity to the exemplary nucleic acid without undue experimentation. Dr. Short declares that it was considered routine by one skilled in the art at the time of the invention to screen for multiple substitutions or modifications of a nucleic acid or a polypeptide for functional variations, including screening for a genus of transaminase-encoding nucleic acids or a genus of transaminases. Dr. Short declares that it was considered routine by one skilled in the art at the time of the invention to screen for subsequences of nucleic acids that can identify or encode enzymes (e.g., transaminases) or enzymatically active fragments of transaminases. Dr. Short declares that it was considered routine by one skilled in the art at the time of the invention to screen for subsequences of nucleic acids that can identify by hybridization a polypeptide-encoding (e.g., transaminase-encoding) nucleic acid.

Whether large numbers of compositions (e.g., nucleic acids, enzymes, antibodies, and the like) must be screened to determine if one is within the scope of the claimed invention is irrelevant to an enablement inquiry. Enablement is not precluded by the necessity to screen large numbers of compositions, as long as that screening is "routine," i.e., not "undue," to use the words of the Federal Circuit. The Federal Circuit in In re Wands directed that the focus of the enablement inquiry should be whether the experimentation needed to practice the invention is or is not "undue" experimentation. The court set forth specific factors to be considered.

One of these factors is "the quantity of experimentation necessary." Guidance as to how much experimentation may be needed and still not be "undue" was set forth by the Federal Circuit in, e.g. Hybritech, Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986). In Hybritech, Inc., a single deposited antibody producing cell line enabled a claim generic to all IgM antibodies directed to a specific antigen. The Federal Circuit noted that the evidence indicated that those skilled in the monoclonal antibody art could, using the state of the art

and applicants' written disclosure, produce and screen new hybridomas secreting other monoclonal antibodies falling within the genus without undue experimentation. The court held that applicants' claims need not be limited to the specific, single antibody secreted by the deposited hybridoma cell line (significantly, the genus of antibodies was allowed even though only one antibody species was disclosed). The court was acknowledging that, because practitioners in that art are prepared to screen large numbers of negatives in order to find a sample that has the desired properties, the screening that would be necessary to make additional antibody species was not "undue experimentation."

Analogously, practitioners of the biological sciences for the instant invention also recognized the need to screen numbers of negatives to find a sample that has the desired properties, e.g., transaminase-encoding activity, or a polypeptide having transaminase activity. Furthermore, as declared by Dr. Short, methods of making and screening procedures used to identify nucleic acids used in the claimed invention were all well known in the art and at the time this application was filed. All were routine protocols for the skilled artisan. Thus, the skilled artisan using Applicants' written disclosure could have practiced the instant claimed invention without undue experimentation.

Applicants respectfully submit that the pending claims meet the enablement requirement under 35 U.S.C. §112, first paragraph. In light of the above remarks, Applicants respectfully submit that the specification sufficiently described how to make and use the claimed methods to satisfy the requirements of 35 U.S.C. §112, first paragraph.

Issues under 35 U.S.C. §112, second paragraph

Claims 42 to 55 and 93 to 106 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite. The instant amendment addresses this issue.

Issues under 35 U.S.C. §102

Henner, et al. (1986) Gene 49:147-152

Claims 42 and 93 are rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Henner.

The legal standard for anticipation under 35 U.S.C. § 102 is one of strict identity. To anticipate a claim, a single prior source must contain each and every limitation of the claimed invention.

The Patent Office alleges that Henner teaches a sequence 50% identical to a fragment of at least 30 or 100 nucleotides of SEQ ID NO:23.

The instant amendment addresses this issue. After entry of the instant amendment, claim 42 will be directed to methods of generating a variant nucleic acid encoding a polypeptide having a transaminase activity comprising obtaining a nucleic acid comprising (a) a sequence as set forth in SEQ ID NO:23, or a nucleic acid encoding an amino acid sequence as set forth in SEQ ID NO:31, (b) sequences complementary to (a), or (c) sequences comprising at least 30 consecutive nucleotides of (a) or (b).

After entry of the instant amendment, claims 93 and 95 will be directed to methods of generating a variant nucleic acid encoding a polypeptide having an aminotransferase activity comprising obtaining a nucleic acid comprising (i) a sequence encoding a polypeptide having an aminotransferase activity and having at least 70% sequence identity to an amino acid sequence as set forth in SEQ ID NO:31, or a nucleic acid having at least 70% sequence identity to a nucleic acid sequence as set forth in SEQ ID NO:23 encoding a polypeptide having an aminotransferase activity (ii) sequences complementary to (i), (iii) a sequence comprising at least 30 consecutive nucleotides of a sequence encoding a polypeptide having an aminotransferase activity and having at least 70% sequence identity to an amino acid sequence as set forth in SEQ ID NO:31, or a nucleic acid having at least 70% sequence identity to a nucleic acid sequence as set forth in SEQ ID NO:23 encoding a polypeptide having an aminotransferase activity, or (iv) a sequence comprising at least 30 consecutive nucleotides of sequences complementary to (iii).

Accordingly, because Henner does not teach a nucleic acid used in the claimed methods, it is not a single prior source that contains each and every limitation of the claimed invention, and the rejection under 35 U.S.C. § 102 can be properly withdrawn.

Issues under 35 U.S.C. §103

Henner in view of Short

Claims 42 to 55, 93 and 94 are rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Henner in view of Short.

The Patent Office alleges that Henner is defective in that it does not teach the methods of mutagenesis specifically recited in claims 42 to 55, 93, and 94.

However, Applicants respectfully aver that Henner is further defective in that it does not teach a nucleic acid used in the claimed methods. Because Short does not teach a nucleic acid used in the claimed methods, it cannot cure the defect in Henner. Accordingly, Henner in view of Short does not teach or suggest the claimed invention.

CONCLUSION

In view of the foregoing amendment and remarks, it is believed that the Examiner can properly withdraw the rejections of the pending claims. Applicants believe all claims pending in this application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

Applicants believe that no additional fees are necessitated by the present response and amendment. However, in the event any such fees are due, the Commissioner is hereby authorized to charge any such fees to Deposit Account No. 03-1952. Please credit any overpayment to this account.

As noted above, Applicants have requested a telephone conference with the undersigned representative to expedite prosecution of this application. After the Examiner has reviewed the instant response and amendment, please telephone the undersigned at 858 720 5133.

Dated: August 17, 2004

Respectfully submitted,

By _____

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